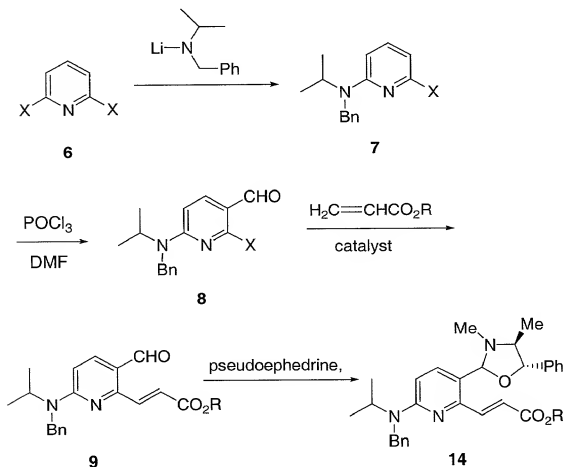


from the group consisting of aryl, CO_2R^4 , CF_3 , $\text{N}(\text{R}^5)_2$, $(\text{C}_1\text{-C}_8)\text{-alkoxy}$, $(\text{C}_1\text{-C}_8)\text{-alkyl}$, $(\text{C}_2\text{-C}_8)\text{-alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_3\text{-C}_8)\text{cycloalkyl}$, $\text{CO}(\text{CH}_2)_n\text{CH}_3$, and $\text{CO}(\text{CH}_2)_n\text{CH}_2\text{N}(\text{R}^5)_2$; and n is 0 to 5.

- 5 Reaction Scheme B below shows a method for the preparation of α , β -unsaturated ester involving an amination, a formylation and a Heck reaction.

REACTION SCHEME B



10

X = halo; R = $(\text{C}_1\text{-C}_6)\text{-alkyl}$

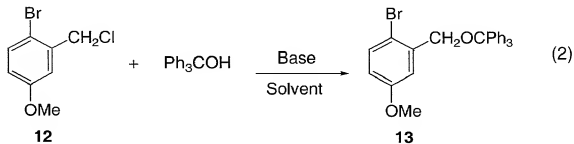
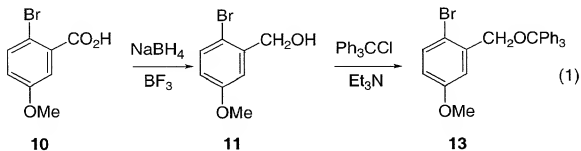
- 15 Commercially available disubstituted pyridine (6) is aminated by lithium N-isopropylbenzylamide to afford the compound (7). The aminated compound (7) was then regiospecifically formylated to give aldehyde compound (8) upon treatment with about 4 equivalents of POCl_3 in dimethylformamide (DMF) at a temperature range of about 35°C to about 70°C . The aldehyde compound (8) then undergoes a Heck

reaction with 1 to 5 equivalents of (C₁-C₆)-alkyl acrylate in the presence of an aprotic solvent, a base and a catalyst at a temperature range of 80°C and 110°C to provide the unsaturated ester (9) in high yield. The unsaturated ester (9) is then reacted with a chiral additive such as pseudoephedrine or N-methyl-cis-aminoindanol (not shown in the scheme) to give the protected aldehyde (16).

The aprotic solvent for a Heck reaction is selected from dimethylacetamide (DMAC), dimethylformamide (DMF), toluene and acetonitrile, and a base is selected from CH₃COONa, CH₃COONa•3H₂O and NaHCO₃. Preferred solvent and base are DMAC and CH₃COONa•3H₂O, respectively. Water may be added (about 6 equivalents) to the reaction mixture to enhance the reaction rate. For example, the reaction rate in the presence of CH₃COONa with water is 6 hours, whereas the reaction without water is 20 hours. The catalyst for the reaction is selected from PdCl₂(dppf)₂, PdCl₂(PPh₃)₂, Pd(dba)₂, PdBr₂, Pd(OAc)₂, and (allyl)₂PdCl₂ dimer with tri-o-tolylphosphine. Preferred catalyst is PdCl₂(dppf)₂.

Another aspect of the invention involves the synthesis of a bottom piece (13), ArX (X is halo), of the compound according to Reaction Scheme C.

REACTION SCHEME C



In Reaction Scheme C, the bottom piece of 2-bromo-5-methoxybenzyl trityl ether (13) can be prepared either by a route (1) or a route (2). The route (1) involves a two-step

synthesis via a reduction and a protection, whereas the route (2) provides a one-step synthesis by using commercially available benzyl chloride (12) in the presence of a base and an aprotic solvent. The base is selected from potassium *tert*-butoxide, KOH or NaH, and the solvent is selected from DMAC, DMSO or DMG. A mixture of potassium *tert*-butoxide and dimethyl acetamide (DMAC) is preferred. The compound (13) can be readily isolated by addition of water. As shown in Table 2 below, the optimal charge ratio of benzyl chloride (12):Ph₃COH:*tert*-BuOK is 1:1.1:1.05 with slow addition of the benzyl chloride.

10 Table 2. Preparation of 2-bromo-5-methoxybenzyl trityl ether (13)

Entry	Ph ₃ COH (eq)	12 (eq)	<i>t</i> -BuOK (eq)	Addition of 12	Yield, 13 (% yield)
1	1.1	1.0	1.05	1h	87%
2 ^a	1.1	1.0	1.05	1h	82%
3	1.0	1.05	1.0	1h	82%
4	1.1	1.0	1.05	5 min	79%

^a1% water is added to DMAC